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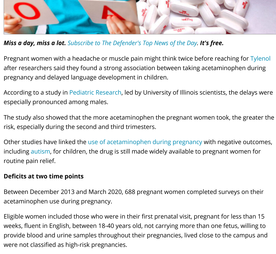
Tylenol Use During Pregnancy Linked to Delayed Language Development

Boys whose mothers took the over-the-counter painkiller acetaminophen experienced delayed speech development at two time periods in early childhood, according to a study in Pediatric Research. *The more acetaminophen mothers took, and the later in pregnancy, the greater the effect.*

By Angelo DePalma, Ph.D.



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Pregnant women with a headache or muscle pain might think twice before reaching for Tylenol after researchers said they found a strong association between taking acetaminophen during pregnancy and delayed language development in children.

According to a study in Pediatric Research, led by University of Illinois scientists, the delays were especially pronounced among males.

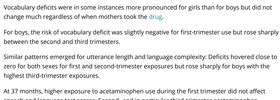
The study also showed that the more acetaminophen the pregnant women took, the greater the risk, especially during the second and third trimesters.

Other studies have linked the use of acetaminophen during pregnancy with negative outcomes, including autism, for children, the drug is still made widely available to pregnant women for routine pain relief.

Deficits at two time points

Between December 2013 and March 2020, 688 pregnant women completed surveys on their acetaminophen use during pregnancy.

Eligible women included those who were in their first prenatal visit, pregnant for less than 15 weeks, fluent in English, between 18-40 years old, not carrying more than one fetus, willing to provide blood and urine samples throughout their pregnancies, lived close to the campus and were not classified as high-risk pregnancies.



From among those women able to provide acetaminophen dosing information investigators enrolled newborns for follow-up language assessment. All subjects were part of the Illinois Kids Development Study (IKIDS), a prospective study of the effects of gestational exposure to environmental chemicals on neurodevelopment.

The researchers assessed 298 children for language development at around 27.5 months of age using the MacArthur-Bates Communicative Development Inventories, and 254 children at about 37 months using the Speech and Language Assessment Scale.

MacArthur-Bates is an early-language assessment instrument that focuses on early comprehension and nonverbal gestures, through vocabulary acquisition and expansion and early grammar development.

MacArthur-Bates uses separate "Words and Gestures" and "Words and Sentences" modules.

The Speech and Language Assessment Scale is a 19-item parent questionnaire to identify children with delayed speech and/or language by assessing linguistic assertiveness, responsiveness, semantics, syntax, articulation and talkativeness.

Among participants in the IKIDS study, 71% of mothers had used acetaminophen at least once during pregnancy, which is higher than the percentage among the general population.

Mothers of children tested by MacArthur-Bates at 27.5 months and those assessed through the Speech and Language Assessment Scale at 37 months took approximately the same amount of acetaminophen while they were pregnant.

More subjects who took acetaminophen while pregnant were white and native English speakers. Although investigators mentioned this as a possible limitation in their discussion, they concluded it did not affect their results.

Patterns emerged at 27.5 months between delayed language development and the reported trimester of acetaminophen use.

When results from boys and girls were analyzed together a modest dose-related trend appeared: The more acetaminophen a woman took during pregnancy, and the later she took it, the greater the delay or deficiency in vocabulary acquisition, utterance length and speech complexity.

Vocabulary deficits were in some instances more pronounced for girls than for boys but did not change much regardless of when mothers took the drug.

For boys, the risk of vocabulary deficit was slightly negative for first-trimester use but rose sharply between the second and third trimesters.

Similar patterns emerged for utterance length and language complexity: Deficits hovered close to zero for both sexes for first and second-trimester exposures but rose sharply for boys with the highest third-trimester exposures.

At 37 months, higher exposure to acetaminophen use during the first trimester did not affect speech and language test scores. Second- and in particular third-trimester acetaminophen exposure lowered scores, but only for boys.

Small but naggingly persistent findings

None of the exposure-development effects were very large but they add to a significant existing literature on acetaminophen and childhood development.

In addition to language deficits, a Norwegian study found poorer motor development and internalization or externalization behaviors in 3-year-old children whose mothers took acetaminophen for 28 days while pregnant.

Another study, also on 3-year-olds, found similar, modest effects of prenatal exposure for acetaminophen but not for opioid painkillers. A third study of long-term gestational exposure found diminished motor and communication skills in 18-month-olds.

These three studies, cited by the authors of the paper in Pediatric Research, used the Ages & Stages Questionnaires, which covers many of the same language competencies as MacArthur-Bates or Speech and Language but is less comprehensive.

Where earlier acetaminophen-language development studies also looked at dosage and extent of developmental delay they did not (or could not) determine when during pregnancy the exposure occurred.

The authors of the Pediatric Research study determined exposure times reasonably accurately by questioning expectant mothers six separate times during their pregnancy.

This led them to conclude that the second and third trimesters may be "windows of neurodevelopment particularly sensitive to disruption of language development by prenatal acetaminophen exposure."

The authors explained that the inner ear and nerves responsible for conveying sounds from the ear to the brain develop during the second trimester, which is when fetuses begin to hear and respond to sounds. The brain also develops rapidly during the second trimester.

"All of this lays the groundwork for further development and maturation necessary for language processing and acquisition," they wrote.

Another possible explanation is that acetaminophen — whose pain-killing mechanism is still poorly understood — works through the endocannabinoid system which participates in several aspects of neurodevelopment, including cell differentiation, cell migration and the formation of new nerve cells.

One of the study's limitations was the large number of women who dropped out during the study. Those who stuck it out tended to be white, non-Hispanic, well-educated, and with high household incomes, so results may not apply to more diverse populations.

Finally, researchers could not rule out that conditions leading pregnant women to take acetaminophen (for example headache, muscle pain) may themselves be risk factors for suboptimal neurodevelopment in their offspring.

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Doctor group's call to action

It has been known since the early 1980s that acetaminophen crosses the placental barrier, meaning that any analysis of exposure risk should include developing fetuses as well as mothers.

Any number of adverse effects might follow given that the drug is toxic to the liver, which in the unborn is a significant source of new blood cells. Acetaminophen overdose is involved in half of all U.S. cases of liver failure and is responsible for 20% of all cases requiring liver transplantation.

Language deficits are by no means the only observed consequence of acetaminophen exposure, and the womb is not the only place where dosing is dangerous.

Acetaminophen exposure in babies has long been associated with developing asthma, dermatitis (skin rash) and allergic rhinitis.

A 2013 paper reported that children who took acetaminophen during their first year were at double the risk of dermatitis, 66% higher risk for asthma and 70% higher risk for rhinitis. This study found similar increases in infants who took antibiotics but the risk was not higher for children who took both drugs.

By 2021, enough evidence of the riskiness of gestational acetaminophen exposure had accumulated that the American College of Obstetricians and Gynecologists published "a call for precautionary action" on acetaminophen and pregnancy.

Among the physician group's recommendations for the design of future epidemiologic studies:

- Controlling for genetic factors to distinguish children at higher inherent risk from those whose only risk is exposure to acetaminophen.
- Accurate capturing of outcomes as they relate to specific exposures.
- Greater focus on timing, dosage and duration of exposure both before and after birth.
- Controlling for the reason(s) acetaminophen was recommended or used. This precaution eliminates the possibility that some conditions for which pregnant women take acetaminophen may themselves be risk factors for development issues in their offspring.

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